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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/344,189	06/24/1999	CHARLES E. ROGLER	0342/1D888US	8764

7590 03/26/2003

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	27

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/344,189	ROGLER, CHARLES E.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/6/03 has been entered.

Applicant's amendments received on 11/7/02 and 1/6/03 have been entered.

Claims 1, 8, 13, 15, 22, 25, 34, 37 and 39 have been amended. Claims 42-48 have been added. Claims 1-48 are pending and are under current consideration.

Drawings

New corrected drawings are required in this application because of the draftsman's objections as set forth in the PTO 948 attached to the office action mailed on 9/12/00. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-13, 15-22, 24-34, 36-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claims to the extent of the compatible hepatitis virus being hepadnavirus or hepatitis D virus coinfected with hepadnavirus, does not reasonably provide enablement for the claims with respect to any other hepatitis virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a chimeric mouse model system for hepatitis comprising an immunotolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunotolerant mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with a compatible mammalian hepatitis virus. The claims further embrace methods of making and using the same mouse.

The specification discusses that the invention features a chimeric mouse model for hepatitis. The specification discusses that the invention features an immunotolerant mouse, lacking functional B and T cell, which has a degenerated liver due to the

expression of a uPA gene present in its genome, wherein mammalian hepatocytes are transplanted into the parenchyma of the degenerated liver to create a chimeric liver, wherein the chimeric liver comprises endogenous and xenogenic hepatocytes. The specification asserts that such a mouse can be a model for any type of hepatitis virus, provided that the xenogenic hepatocytes and hepatitis virus are compatible. While the specification provides extensive teachings pertaining to such a mouse as a model for hepadnavirus and hepatitis D virus coinfected with hepadnavirus, wherein the uPA transgene present in the genome of said mouse is hemizygous or homozygous, the specification fails to provide any relevant teachings or specific guidance with regard to such a mouse as a model of other hepatitis viruses as embraced by the claims. In particular, the specification has not provided guidance for the other models of hepatitis with regard to the genotype of the uPA gene present in the genome of such a mouse. More particularly, the specification has not provided guidance that correlates the genotype of the uPA gene present in the genome of such mouse with infection of xenogenic hepatocytes by a compatible hepatitis virus, wherein the compatible hepatitis virus is other than hepadnavirus or hepatitis D virus coinfected with hepadnavirus. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed.

While the specification has provided guidance for a chimeric mouse of the invention that is a model for hepadnavirus and hepatitis D virus coinfected with hepadnavirus the specification has not provided relevant teachings or guidance for chimeric mice that models for the other hepatitis viruses embraced by the claims. The

specification has contemplated that such a mouse could be used as a model of other hepatitis viruses. However, the specification has failed to provide guidance for creating models of other hepatitis viruses embraced by the claims using the chimeric mouse of the invention, in particular the specification has not provided guidance with regard to the genotype of the uPA gene in the genome of the mouse which is necessary to support infection of the xenogenic hepatocytes by the other hepatitis viruses. Moreover, the specification has failed to provide any guidance, working examples, or relevant teachings that would allow the skilled artisan to use hepatitis viruses other hepadnavirus or hepatitis D virus coinfected with hepadnavirus when practicing the claimed invention. The specification has taught that chimeric mice, which are used as models for hepadnavirus or hepatitis D virus coinfected with hepadnavirus may be hemizygous or homozygous for a uPA transgene contained within the genome of said mouse. The specification however, has failed to provide any correlation between the genotype of uPA (hemizygous or homozygous) and infection of xenogenic mammalian hepatocytes contained in the chimeric mice with other hepatitis viruses to create the other models of hepatitis embraced by the claims such that the skilled artisan could extrapolate use of hepadnavirus or hepatitis D virus coinfected with hepadnavirus to use of other hepatitis viruses. The state of the art suggests that specific guidance with regard to the genotype of uPA transgene in chimeric mice is necessary for creating models of hepatitis. Mercer et al (Nature Medicine, 2001, 7(8): 1-7; IDS document AQ) report that in a chimeric mouse model for hepatitis C virus (HCV) only a mouse homozygous for the uPA transgene could support infection of human hepatocytes with HCV. See page 2,

columns 1-2 and the paragraph bridging to page 3. Mercer et al further report that HCV was not detectable in hemizygous uPA chimeric mice but was consistently detected in homozygous uPA chimeric mice. The specification however, has not provided specific guidance that correlates uPA homozygous chimeric mice with HCV infection. The specification has asserted that either hemizygous or homozygous uPA mice could be used to create a hepatitis model. Accordingly, it appears that a level of unpredictability exists with regard to the ability of the chimeric mice to support hepatitis infection that is directly correlated with the uPA transgene. The specification has failed to provide guidance that overcomes the unpredictability in the art related to the uPA transgene by failing to correlate the uPA genotype with hepatitis virus infection for hepatitis viruses other than hepadnavirus or hepatitis D virus coinfected with hepadnavirus. A mere statement that other hepatitis viruses exist and could be used is not sufficient to enable the breadth of the claims as directed to any other hepatitis virus that infect xenogenic mammalian hepatocytes in a chimeric mouse. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. In this case the starting material that has not been disclosed is the genotype of the uPA transgene necessary to support hepatitis virus infection of xenogenic mammalian hepatocytes in a chimeric mouse embraced by the claims other than hepadnavirus or hepatitis D virus coinfected with hepadnavirus.

Claim 39 (and the claims that depending from it) do not recite hepatitis virus or infection of xenogenic mammalian hepatocytes with hepatitis virus. The specification however has not provided any other uses for the chimeric mice embraced by the claims other than to serve as models of hepatitis. As such the specification has failed to provide guidance that correlates to purposes, other than hepatitis models, for creating the chimeric mice of the invention.

Given the lack of guidance provided by the instant specification with regard to the other hepatitis viruses it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Note: Amending the claims such that they are directed to hepadnavirus or hepatitis D virus coinfected with hepadnavirus may be sufficient to overcome this rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 13-37, 39-42, 44-46 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete as written. The claim is directed to a method of making a chimeric mouse. However, the claim is incomplete because the steps of the method do

not relate back to the preamble in a positive process. Appropriate correction is required. Claims 2-7 and 42 depend from claim 1.

Claims 13, 22, and 34 lack antecedent basis for the recombination activation gene 2 (RAG-2) knockout gene. Additionally, the meaning of recombination activation gene 2 (RAG-2) knockout gene is unclear and unsupported by the specification as the specification has not provided a definition for a recombination activation gene 2 (RAG-2) knockout gene. Claim 14 depends from claim 13. Claim 23 depends from claim 22.

Claim 15 is incomplete as written. The claim is directed to a method for screening a test compound for anti-viral activity. However, the claim is incomplete because the steps of the method do not relate back to the preamble in a positive process. Appropriate correction is required. Claims 16-24 and 44 depend from claim 15.

Claim 25 is incomplete as written. The claim is directed to a method for screening a test compound for anti-cancer activity. However, the claim is incomplete because the steps of the method do not relate back to the preamble in a positive process. Appropriate correction is required. Claims 26-36 and 45 depend from claim 25.

Claim 37 is incomplete as written. The claim is directed to a method of making a chimeric mouse. However, the claim is incomplete because the steps of the method do not relate back to the preamble in a positive process. Appropriate correction is required. Claim 46 depends from claim 37.

Claim 39 is incomplete as written. The claim is directed to a method of making a chimeric mouse. However, the claim is incomplete because the steps of the method do not relate back to the preamble in a positive process. Appropriate correction is required. Claims 40-41 and 48 depend from claim 39.

Allowable Subject Matter

Amending the claims to the extent that they read on hepadnavirus and hepatitis D virus coinfected with hepadnavirus may be sufficient to place the instant application in condition for allowance.

Conclusion

No claim is allowed. The claims appear to be free of the prior art of record but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER